

Case Report

Probable Valproate Sodium–Associated Hypotension

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ABSTRACT

Background: Valproate sodium, a commonly used antiepileptic drug (AED), is effective for the treatment of status epilepticus and is often used as a second-line agent when other AEDs are contraindicated. Some studies have reported that infusion of valproate sodium is generally well tolerated, whereas other studies have reported various degrees of hypotension during infusion. The objective of this case report was to call attention to the potential risk of hypotension after intravenous infusion of valproate sodium.

Case summary: This was the case of a 75-year-old Hispanic man (height, 145 cm; weight, 68 kg) who developed hypotension after receiving an intravenous loading dose of valproate sodium. The patient received the loading dose 12 hours after administration of his last dose of phenytoin (300 mg daily), which had been discontinued secondary to a cutaneous drug reaction. The patient's medical history was significant for seizure disorder, a cerebrovascular accident, and controlled type 2 diabetes mellitus. He was taking glyburide 5 mg daily and aspirin 81 mg daily. At baseline, the patient's blood pressure (measured while seated, at rest, using an upper-extremity cuff) was 135/70 mm Hg. The intravenous loading dose of valproate sodium (20 mg/kg) was administered at a rate of 14 mg/min (total dose, 1280 mg over 90 min). Approximately 2.5 hours after completion of the loading dose, the patient's blood pressure decreased to 107/48 mm Hg. Because our standard operating procedure is to measure blood pressure every 4 hours after the baseline measurement, the patient's hypotension was not detected during the infusion. The next morning (22 hours after completion of the valproate sodium infusion), divalproex sodium 1000 mg orally once daily was initiated as maintenance therapy. The patient's blood pressure reached a nadir of 82/44 mm Hg. The hypotension was treated initially with intravenous fluid hydration with normal saline, but the blood pressure correction was transient using this approach. The patient remained hypotensive for 3 days. The hypotension was ultimately found to be self-limited, and the patient was asymptomatic throughout his hospital stay. The patient's Naranjo adverse drug reaction probability scale score was 6, indicating that the relationship between valproate sodium infusion and hypotension was probable.

Conclusion: In this case report, infusion of valproate sodium at a rate of 14 mg/min was a probable cause of hypotension in a 75-year-old man. (*Am J Geriatr Pharmacother.* 2010;8:281–284) © 2010 Excerpta Medica Inc.

Key words: valproate, hypotension, geriatric, antiepileptic drug.

Accepted for publication March 30, 2010.

Published online April 26, 2010.

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doi:10.1016/j.amjopharm.2010.04.005

1543-5946/\$ - see front matter

INTRODUCTION

Intravenously administered valproate sodium* has been reported to be an effective agent for the treatment of status epilepticus, acute repetitive seizures, and epilepsy in patients who are not actively manifesting seizures.¹⁻³ This agent is also recommended when use of traditional antiepileptic drugs (AEDs) is contraindicated.⁴ Although valproate sodium infusion is considered to be generally well tolerated,⁵ studies have reported varying effects of the drug on blood pressure.⁶⁻⁸ Although some studies have reported no association with decreased blood pressure during infusion,^{1,2} others have reported associated hypotension^{6,7} and even circulatory collapse during infusion.⁸

The objective of this case report was to call attention to the potential risk of hypotension after intravenous infusion of valproate sodium. The PubMed database was searched for articles published between 1980 and August 2009 that contained the terms *valproate* and *hypotension*. Only 3 articles that discussed valproate-associated hypotension were identified.⁶⁻⁸

CASE SUMMARY

A 75-year-old Hispanic man (height, 145 cm; weight, 68 kg) was admitted to the medicine service by his neurologist for administration of a loading dose of valproate sodium 12 hours after discontinuation of phenytoin therapy secondary to a diffuse, pruritic, and exfoliative dermatitis that covered his neck, trunk, and both upper extremities. The remainder of his physical examination was unremarkable. The patient originally received phenytoin maintenance therapy after an episode of status epilepticus secondary to ischemic stroke. The patient had no recurrence of seizures after initiation of phenytoin. However, after 4 months of phenytoin therapy, he began to notice the cutaneous drug reaction. The reaction worsened progressively over the course of 10 days, at which point the phenytoin was discontinued. The patient was afebrile and had no constitutional symptoms. The exfoliative dermatitis was accompanied by eosinophilia (22.7%; normal, 0%–7%). Blood chemistry and liver function tests were within normal limits (albumin, 3.7 g/dL; alanine aminotransferase, 37 IU/L; aspartate aminotransferase, 42 IU/L; total bilirubin, 0.8 mg/dL; international normalized ratio, 1.0). In addition to his seizure disorder, the patient had a medical history significant for a cerebrovascular accident in 2008 and type 2 diabetes mellitus controlled with glyburide 5 mg daily. His only other concomitant medication was aspirin 81 mg daily.

On the same day that phenytoin was discontinued, the patient was advised to come to the hospital for a loading dose of valproate sodium and overnight observation. Immediately before the infusion, the patient's blood pressure was 135/70 mm Hg. According to records from previous office visits, which dated back to 2 months before this hospital admission, he had stable blood pressure readings, ranging from 132/72 to 136/70 mm Hg. Blood pressure in the office visit setting was measured in the same manner as in the hospital (ie, seated, at rest, using an upper-extremity cuff). The loading dose of valproate sodium was 20 mg/kg, and the infusion rate was 14 mg/min (total dose, 1280 mg over 90 min). Approximately 2.5 hours after completion of the infusion, the patient's blood pressure decreased to 107/48 mm Hg. Because our standard operating procedure is to measure blood pressure every 4 hours after the baseline measurement, the patient's hypotension was not detected during the infusion. The next morning (day 2), 22 hours after completion of the valproate sodium infusion, divalproex sodium† 1000 mg orally once daily was initiated as maintenance therapy. Throughout day 2, the patient had consistent blood pressure readings, ranging from 82/44 to 98/52 mm Hg.

The following morning (day 3), a 1-L bolus of normal saline was administered intravenously because the patient was still hypotensive. No laboratory data were available to determine whether the patient was dehydrated, but the patient's blood pressure increased to 145/72 mm Hg after administration of the fluid bolus. This change was transient, however, because the patient's blood pressure decreased to 92/54 mm Hg in <6 hours. The next day (day 4), the patient's blood pressure was monitored without further intervention because the patient had no symptoms related to hypotension. Over the course of the day, his blood pressure rose to 115/65 mm Hg. The next morning (day 5), his blood pressure was 132/72 mm Hg and remained stable until early afternoon. Given that his return to baseline blood pressure was sustained, the hypotension was considered to be self-limited and the patient was discharged home.

Of note, during the patient's entire hospital course, his heart rate ranged from 65 to 78 beats/min. Moreover, he was not thought to be clinically dehydrated because he had no physical signs of dehydration; he consumed water by mouth regularly and completed 100% of his meals. He had no complaints of chest pain, shortness of breath, or presyncope.

*Trademark: Depacon® (Abbott Laboratories, North Chicago, Illinois).

†Trademark: Depakote® (Abbott Laboratories).

The Naranjo adverse drug reaction probability scale⁹ was used to assess the probability of valproate sodium-associated hypotension. The patient had a Naranjo score of 6, which indicated a probable association.

DISCUSSION

The actual risk of valproate sodium-induced hypotension is not clearly defined in the literature.⁵ In this case report, an elderly patient experienced hypotension for ~3 days; the hypotension began ~2.5 hours after a 90-minute infusion of valproate sodium. A 1-L intravenous bolus of normal saline resolved the hypotension temporarily, but ultimately, the hypotension was found to be self-limited.

Currently, the US Food and Drug Administration does not approve an infusion rate of >20 mg/min for valproate sodium. Nevertheless, the effects of more rapid infusion of this AED have been studied. Limdi and Faught⁶ reported 5 patients (25% of a cohort of 20) aged 32 to 56 years who experienced some degree of decreased blood pressure with infusion of valproate sodium (83.3–555.0 mg/min). Two of these patients required administration of metaraminol, whereas the hypotension in the other 3 patients resolved without intervention. White and Santos⁷ reported a case of an 11-year-old girl who also required vasopressor therapy to correct significant hypotension that occurred during infusion of valproate sodium at a rate of 16 mg/min. Kumar et al⁸ published a case report describing a hemodynamically unstable 5-year-old girl who required full resuscitation after developing circulatory collapse during an infusion of 480 mg of valproate sodium at a rate of 24 mg/min. However, it should be noted that this pediatric patient was already receiving vasopressor support before infusion of valproate sodium.

Pharmacologic intervention was not necessary in the present case. Although the patient's hypotension was ultimately not life threatening, the duration of the blood pressure decline was unpredictable at the time of his hospital stay. Based on the results of the literature review, the slowest infusion rate that was associated with hypotension before publication of this case report was 16 mg/min.⁷ The patient in this case developed hypotension after receiving a loading dose of valproate sodium at a rate of 14 mg/min (total dose, 1280 mg over 90 min).

The patient in this case report had a Naranjo score of 6, indicating a probable association between the valproate sodium infusion and hypotension. There are no data at this time to suggest that the patient's hy-

potension may have been attributable to discontinuation of phenytoin, the patient's coexisting medical conditions, or the use of glyburide and aspirin. In addition, it is unclear whether the maintenance doses of divalproex sodium may have contributed to the prolongation of the hypotension. This is doubtful, however, because the patient continued the divalproex sodium regimen after his hypotension had resolved.

Valproate sodium is metabolized primarily by the liver and has a half-life of ~16 hours.¹⁰ The other major area of metabolism is in the mitochondria. A minimal amount of the drug is excreted unchanged in the urine. Although the patient discussed in this case report had no known liver disease, it is important to consider a patient's liver function status before administering valproate sodium, given these pharmacokinetic properties. This patient's liver function tests were within normal limits, but evidence suggests that age-related decreases in valproate metabolism and clearance may occur in older adults.¹¹

One hypothesis to consider is that the long half-life of valproate sodium, the intravenous administration of the AED, and the advanced age of this patient, in concert, may have contributed to the hypotension. Another hypothesis is that there may have been a higher concentration of unbound, infused valproate sodium secondary to the remaining concentration of protein-bound phenytoin that had not yet been eliminated from the patient's systemic circulation, which may have allowed freely circulating valproate to have an increased influence on systemic blood pressure.

The actual mechanism by which valproate sodium infusion may have caused this patient's hypotension is unknown. Interestingly, some studies of adult and pediatric cohorts have reported no occurrence of hypotension associated with valproate sodium infusion.^{1–3} However, conflicting data that hypotension may be associated with valproate sodium infusion exist in the literature.^{6–8} Given the varied findings from this literature review and case report, blood pressure surveillance of elderly patients during and after valproate sodium infusion may be recommended.

CONCLUSION

In this case report, valproate sodium infusion at a rate of 14 mg/min was a probable cause of hypotension in a 75-year-old man.

ACKNOWLEDGMENT

The author has indicated that he has no conflict of interest regarding the content of this case report.

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